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The Biological and Toxin Weapons Convention

Implications of Advances in Science and Technology

Conference Report

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The Biological and Toxin Weapons Convention

Implications of advances in
science and technology

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This summary is designed as a record of issues that were discussed during the international workshop on advances in science and technology for the BWC, held 13 – 15 September 2015. The views expressed are those of the authors and do not necessarily represent the consensus opinions of workshop participants, the organizations that provided support for the project, or the 107 academies of science that form IAP nor mention of trade names, commercial practices, or organisations imply endorsement by the US or UK governments or other sponsors. Biosecure was commissioned to produce the background documents and initial drafts of the report documents.

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Introduction

In preparation for the 8th Review Conference, a meeting comprising 72 delegates from 30 countries was convened in Warsaw in September 2015 to identify and discuss trends in science and technology relevant to the Biological and Toxin Weapons Convention. The conference noted many issues of relevance to the Review Conference and reached several overarching conclusions.

Developments in science and technology and the BWC

The upcoming Review Conference will consider whether there had been any novel developments since the Seventh Review Conference that could either enable activities inconsistent with the aims and objectives of the treaty, or which would not be covered by the BWC (Article I) or additional understandings reached at subsequent review conferences.

No concrete examples of such developments were identified either through the literature reviews or in workshop discussions.

However, a number of potential future scenarios were identified that do give cause for concern. Situations where, for example, the mechanisms of action of weapons are not clearly ‘chemical’ or ‘biological’, where components are significantly different from existing biological systems, or where inorganic materials mimic biological function, thereby having a biological effect.

It was easy to envisage how progress in areas such as the convergence of the sciences, nanotechnology and therapeutic design, might lead to such consequences. States Parties could proactively consider the implications of these scenarios before they can be realised, thereby providing a window of opportunity to develop appropriate responses and actions.

Given the increasing pace of progress and the additional possibility of sudden ‘non-linear’ advances in research fields, it is difficult to estimate when such potential scenarios might become relevant to the BWC. Further consideration of progress in this area may be needed prior to the 9th Review Conference and this reinforces the importance of a flexible process for on-going reviews (see page 7).

Biotechnology is an increasingly important global manufacturing technology. Degrading manufacturing infrastructure and capability has long been a tool of war, insurgency and armed conflict. The ‘bio-economy’ itself is therefore a potential target for biological weapons. The BWC currently prohibits weapons that cause harm to human, animals and plants and it should be explored whether there are any risks, not already captured by existing treaties and laws, of weapons that cause damage to equipment, supplies, or material associated with the bio-economy.

The conference also noted an increased need for education and outreach to promote the aims and objectives of the BWC amongst the scientific community as well as the provision of responsible mentorship for early-stage researchers. There are already some examples of excellence in this area (see Box 1) but more effort is needed by States Parties and ‘best practices’ disseminated.

Box 1: An example of excellence in socially responsible scientific mentorship (Synbio LEAP)

The Leadership Excellence Accelerator Program (LEAP) provides Fellows with mentorship, practical skills and a sustaining network to help them guide a socially responsible future for synthetic biology. It is an incubator for emerging leaders across disciplines and sectors to develop new strategies for biotechnology in the public interest.

LEAP is an intensive year-long non-residential Fellowship program. Each round, twenty fellows participate in two in-residence workshops during which Fellows work together to develop strategies to address their top challenges for the practice of synthetic biology, under the guidance of world-class experts across disciplines and sectors.



Image
Participants at a LEAP meeting at the Wilson Center, Washington DC.
Photo courtesy of David Sun Kong Photography.

Monitoring developments in science and technology

It is clearly desirable for the BWC to ensure that new knowledge and techniques do not facilitate breaches of the treaty, whilst expediting their peaceful applications. This requires an understanding of how developments in the life sciences and biotechnology might impact the treaty.

There is therefore a pressing need for effective, on-going, and suitably resourced arrangements to:

- Formulate specific questions that can be answered by reviewing developments in science and technology;
- Identify current scientific and technical capabilities pertinent to these questions;
- Consider the implications of those development in the context of the BWC; and
- Take decisions or actions necessitated by those developments.

Models used by other international bodies, including disarmament forums, environmental or health treaties could be adapted for this purpose. The advantages and disadvantages of these different formats should be explored in the context of the BWC’s remit.

Whatever processes is eventually implemented, it should be:

- **Flexible** – able to adjust to changing needs and priorities;
- **Inclusive** – able to take advantage of expertise, wherever it is to be found;
- **Agile** – able to adjust quickly to seize all available opportunities;
- **Responsive** – able to actually change when needed;
- **Able to foster greater engagement** – actively encouraging and enabling contributions from the widest possible set of stakeholders; and
- **Transparent** – ensuring the widest possible group of stakeholders benefit from its work.

The conference observed that the development of a technique for systematically assessing the risk of new scientific developments would be of enormous help in assessing the threat of future trends. Such a process might also usefully consider criteria for identifying relevant or significant developments.

The global ability to deal with disease has been enhanced

The meeting noted that our collective capacity to deal with disease has markedly improved since the Seventh Review Conference, regardless of whether the outbreak is naturally occurring or the result of a malevolent act. Several factors have contributed to this.

Understanding disease

Improved understanding of disease mechanisms has increased our capacity to detect, respond to and mitigate outbreaks, regardless of their source. Such developments strengthen capacities relevant to Articles VII and X of the BWC. Particularly noteworthy is our enhanced understanding of transmissibility and host range; pathogenicity and virulence; toxins; unusual disease agents (including prions and fungi); immunology and host-pathogen interactions; the role of the microbiome; and the significance of ‘biofilms’ for pathogen persistence.

Detection of disease

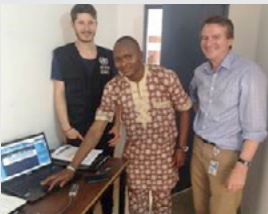
Developments in technology have enabled faster, more accurate detection and characterisation of disease outbreaks facilitating more rapid and effective intervention. These will reduce the impact of an outbreak, regardless of its origin, thus supporting the aims of Articles VII and X of the BWC. In particular, the meeting identified advances in biosensors, biomarkers, mass spectrometry, microscopy and imaging as significant in this respect. More comprehensive baseline data is needed to assist in comparisons and establish a ‘norm’ against which to compare unusual events.

We are increasingly able to differentiate between deliberate and natural outbreaks, using genomics, PCR and mass spectrometry and the emerging discipline of ‘microbial forensics’ can help establish attribution if a malevolent deployment is suspected. Such a finding would entail obligations and commitments by other States Parties under Article VII, as well as additional agreements reached at successive review conferences.

Diagnosis and surveillance

Improvements in diagnostics and disease surveillance can identify causative agents more rapidly, expediting the selection of optimal treatment options and preventing transmission. These developments strengthen capacities applicable to Articles VII and X of the BWC. Relevant improvements here include; rapid diagnosis of unknown pathogens; sequencing; PCR diagnostics; distributed diagnostics (see Box 2) and point-of-care devices; centralisation of certain types of laboratory capacity; genetic and molecular epidemiology; as well as the use of cheap and disposable equipment. Substantial improvements in diagnostic speed and accuracy were noted.

Box 2: Distributed diagnostics



Developments in genetic sequencing technologies have not only made it faster and easier to sequence a genome but have made it possible to do it around the world.

The MinION nanopore sequencer was deployed by the European Mobile Laboratories in Guinea in 2015, as part of an effort to address a large scale Ebola Virus Disease outbreak. This new platform enabled Guinean authorities to obtain important diagnostic and epidemiological information within 48 hours with the samples never leaving the country.

Image
Left: Josh Quick, University of Birmingham, UK. **Center:** Dr. N’Faly Magassouba, Infectious and Tropical Diseases Department, National Hospital Donka, Conakry, Guinea. **Right:** Prof. Miles Carrol, Public Health England, Porton Downs UK.

Preventing, mitigating and treating disease using vaccines and drugs

The timely use of effective vaccines and therapeutics prevents or reduces the impact of outbreaks, regardless of cause. This is of direct relevance to Articles VII and X. Rapid detection and characterization of infectious agents reduces the time required to develop vaccines, drugs and other counter-measures.

Outsourcing of key production steps has reduced the need for dedicated vaccine production infrastructure. It is increasingly simpler, faster and cheaper to industrialize production processes. Single-use equipment and modular production technologies shorten turn-around times. A more distributed production base in industry reduces the distance a product has to travel to its point of use. However, regulatory and liability issues associated with diagnostics, drugs and vaccines in health emergencies continue to limit potential for progress and this is an issue that should be addressed.

High-throughput platforms and ‘big-data’ approaches continue to reveal a wealth of potential new targets and candidates for drugs and vaccines. The design, testing and optimisation processes have been streamlined by the ‘digitalization’ of biology supported by better computational technologies, improved capacity for rational design, integration of synthetic biology approaches, more sophisticated modelling tools, enhanced synthesis technologies and a wider array of platform technologies (see Box 3).

Online laboratories and facilities now offer all of these services at a single site, as an ‘organism design support service’. Throughput has been improved using machine-learning and semantic web-based approaches. Enhanced screening of drug candidates and other enabling tools have helped streamline the development pipeline. However, bioinformatics capabilities remain a major challenge in this area.

Since the Seventh Review Conference, a number of new drug classes have been developed and existing classes of drugs have been further exploited. Examples include: antibody-based drugs; novel drugs for diseases traditionally associated with biological weapons (e.g. anthrax, ricin); the use of drug combinations; drugs to target disease vectors; and in identifying useful off-label indications for existing drugs.

Vaccines have been developed for combating multiple agents or strains by targeting conserved regions and rendered more effective and stable through the use of virus-like particles and improved adjuvants. A number of new avenues for designing vaccines have been explored, utilising synthetic biology, DNA nanostructures and RNA viruses.

Box 3: An example of how the digitization of biology accelerates vaccine development. The Novartis H7N9 influenza vaccine response – Combining synthetic virus generation with flu cell culture platform



Industrialisation of biotechnology

The space and resources required for biologics production has also decreased and the physical size of production equipment has been drastically reduced. Smaller facilities using more compact equipment increases the range of potential sites and reduces logistical challenges, in some cases also offering cost benefits. Scaling-up production to industrial levels has been simplified and can be accomplished more quickly, although it can still take years.

In some cases, the costs of industrial scale-up have fallen, through improved ‘directed evolution’ techniques for example. In other cases, improvements in efficacy and efficiency, such as those associated with automation and miniaturization, may incur increased costs.

Bio-based production and biosynthesis have become common methodologies, aided by particular developments in the use of bacterial and yeast ‘chassis’ and ‘scaffolds’ to control the spatio-temporal arrangement of components. There have been improvements in vaccine expression, in particular through insect cell line and suspended cell cultures and the use of bulk production material.

The increase in usage of disposable or single-use equipment has also been noteworthy. The range of processes for which disposable equipment is available has increased in number and complexity and increasing standardization of parts, facilitates switching to disposable equipment. Disposable or single-use equipment reduces the upfront capital investment required as systems for cleaning and sterilization are not required. They also reduce the chance of cross-contamination, making the systems more efficient.

Outsourcing of production, including the advent of ‘biofabs’, has also become a reality since the Seventh Review Conference. Post-production purification steps have been improved or simplified, as a result of the growing regulatory attention paid to ensuring viral removal or inactivation.

Delivery of drugs

Significant hurdles to storing or shipping labile therapeutics have been overcome. There have been notable successes in replacing cold chains and increasing the environmental stability of vaccines and drugs, in some cases enabling room temperature storage.

Automated design strategies and other tools have made it easier to engineer and tailor drug delivery systems. The range of drug delivery platforms, such as enhanced and novel viral vectors and ‘microneedles’ has increased. Trans-dermal delivery systems are more effective and the range of substances that can be successfully delivered this way has increased since the Seventh Review Conference, opening opportunities for the non-invasive use a wider range of drugs and vaccines. There have also been improvements in targeted delivery systems, ensuring enhanced drug or vaccine access to the desired sites, tissues or cell-types following administration.

Elucidation of nanoparticle structure-function relationships has led to improved drug delivery vehicles. The range of nanoparticle-based drug delivery platforms has increased and now includes formulations that cross barriers and penetrate previously unreachable sites. Nanoparticles can now be designed to enhance the activity of their payload or to overcome its rapid metabolism. This reduces costs and increases efficiency by reducing the amount of payload needed, reducing threshold activity requirements for effective payloads, or prolonging their action by extending their effective life time. Controlled release of payloads, for example by remote activation or environmental response, reduces side effects.

Antimicrobial resistance

The conference noted, however, that past advances in treating disease are being reversed by the increasing antimicrobial resistance. For example, antiviral resistance and resistance to anti-malarial therapies have been growing in both numbers and geographic distribution.

Although the problem remains severe, we now have a better understanding of the mechanisms involved, including the identification and characterization of genetic components, structure-function relationships, metabolic processes, and community responses. Some new drugs have been developed, including additional antimicrobials (comprising both antibiotics and antivirals), therapies to re-sensitize microbes to existing antimicrobials, and drugs to target persistent organisms in biofilms or resistant cells.

Responding to, rolling back, and recovering from disease

The conference noted that the speed at which an outbreak can be terminated and normal life resumed, determines the overall impact of a disease event. These are important considerations for both Articles VII and X of the BWC.

Given the advances listed above, the meeting noted that, provided the remaining logistical, economic and technical challenges can be surmounted, it should now be possible to assemble patchwork capabilities into a diffuse but integrated system for countering global or local outbreaks. Obviously this highly desirable objective would only be successful if backed by political will and the fostering of international support and collaboration.

Such a system could scale from local needs through to international responses. A structure that enabled data, such as pathogen sequences, to be shared more effectively and efficiently would facilitate a rapid and effective response. As expertise and ‘know-how’ matures, opportunities for technological leapfrogging appear, as was the case with mobile communication systems. Developing countries can then access opportunities and capabilities in the field that match, if not surpass, those found in developed countries.

A co-ordinated response to a disease outbreak can only be effective if the communities involved are prepared to work with the emergency responders. Anthropological studies have identified and developed ‘good practice’ guidelines for obtaining community cooperation.

Equally, improved access to drugs and vaccines has enhanced infection control, using, for example, pre-emptive vaccination whilst a more judicious choice of infection control approaches (such as quarantine and travel restrictions) can be matched appropriately to specific situations. ‘Microbial forensics’ can be used to help establish attribution if a malevolent deployment is suspected.

New tools have improved the medical management of disease outbreaks, including intentional releases. Context-specific guidance to optimise response preparedness, for example for the use of anti-microbial drugs and decontamination options is now available. Superior protective equipment is now available, reducing the burden placed on responders and allowing them to work for longer, increasing the efficiency of a response. A wider range of decontaminants, and the optimisation of approaches for developing and using them, have reduced environmental transmission risks and released contaminated sites more quickly.

Advances that reduce risks relevant to the BWC

The conference welcomed a number of developments that reduce overall risks relevant to the BWC. These include:

- Enhanced ability to identify prohibited activities, relevant to Article I;
- More effective barriers to acquiring biological agents for activities prohibited by the BWC in a manner that does not restrict their use for permitted purposes, relevant to Articles III, IV and X;
- Alternatives to capabilities which might be used for prohibited activities without impacting function for permitted purposes, relevant to Articles III and X;
- Alternatives to agents which might be used for prohibited activities without impacting their use for permitted purposes, relevant to Articles III and X; and
- Progress in for identifying activities with potential biosecurity concerns, relevant to Articles III and IV.

Developments in science and technology posing future risks for the BWC

The scientific advances described in this report could also facilitate almost every step of a biological weapons programme and technological barriers to acquiring and using a biological weapon have been conspicuously eroded since the Seventh Review Conference. This has significant implications for Articles I, III and IV of the BWC.

Many of these developments are at the leading edge of current capabilities. They are expensive and complicated to acquire and deploy successfully. Making use of them for prohibited purposes would probably require the resources of a state. This situation may change in the future, reinforcing the need for on-going efforts to review relevant developments in science and technology. Examples of these developments include:

Acquisition of pathogens or toxins

Since the Seventh Review Conference there has been headway in:

- **Acquiring agents from nature;** including an expanded range of possible agents and locations in which they are to be found, as well as tools for characterising previously ‘unculturable’ microbes;
- **Synthesising existing agents;** non-specialists can now compile gene ‘cassettes’ coding for virulence factors and ‘reboot’ some viruses; pathogens responsible for historical epidemics can now be synthesised or reactivated; many small peptides, bioregulators and toxins can now be produced by chemical synthesis;
- **Designing and synthesising novel agents,** using genome engineering platforms, ‘cloud-labs’, ‘biofabs’, and more sophisticated tools, the availability of standards for designing, manipulating and compiling microbes, their parts, and proteins. Novel pathogens have now been produced.

Neurobiology has also seen an exponential increase of output, improving our understanding of neural network responses associated with behaviours, such as anger and aggression, and physiological conditions such as addiction, fear and narcolepsy. Neural networks can now be manipulated to induce some of these states and work has begun to translate these findings to non-human primate models.

The meeting highlighted the potential to develop other novel agents, including those produced using CRISPR/CAS9-mediated ‘gene drives’, ‘gene silencing’ technologies, proteins, or nanoparticles. Some of these types of constructs have already been inserted into vectors and demonstrated to produce effects in a host when administered by inhalation. The potential to target the microbiome to cause or exacerbate a disease state was also noted.

Enhancing virulence of naturally occurring pathogens

Virulence and other biological features of pathogens are now more easily optimised for use in biological weapons and some ‘enhanced pathogens’ have been produced. This has been made possible by improvements in:

- Identification and characterization of the genetic components and key structural elements controlling pathogenicity, transmissibility, host range, antimicrobial defences, drug resistance as well as in the mechanisms through which pathogens avoid the host’s immune system;
- Applying an improved understanding of immunopathology to module the immune responses in a host;
- Using coatings and shells to confer environmental stability; and
- Developing tools for identifying and integrating desirable factors into biological agents.

Modern genome ‘editing’ technologies, such as CRISPR/CAS-9 often do not leave ‘fingerprints’ indicating that that organisms has been altered. This conceals attempts to enhance the organism’s effectiveness, hampers forensic investigations and complicates the differentiation between unusual and unnatural disease events. Some methodologies do leave ‘fingerprints’, in particular, the use of a gene drive as the ability to be passed on to the next generation is due to a permanent change to the organism. (see Box 4).

Box 4: An example of a novel biological agent to target plant and animal populations

The development of CRISPR-based ‘gene drives’ could enable individual laboratories to unilaterally alter the traits of wild populations and ecosystems without regard for national borders. Hundreds if not thousands of laboratories will have this capability within a few years. In principle, alterations can be undone by subsequent gene drive countermeasures, but must first be detected by environmental monitoring of at-risk species. This clearly requires detailed knowledge of whether those species can be affected.

There are currently only a handful of laboratories working in the CRISPR-gene drive field.

Representatives of these groups as well as those in related areas have already called for transparency and safeguards to prevent accidental releases. Researchers in the field are now calling for all CRISPR gene drive research to publicly disclose experimental designs and safeguards against accidental release in advance of experiments. Transparency will ensure compliance with the BWC, accelerate the science by encouraging international collaborations, and promote early deliberations and community guidance of potential applications in public health, sustainable agriculture, and ecological conservation.

Toxins

The genetic components and mechanisms of action of toxins are increasingly well characterised. More sophisticated tools for researching and manipulating toxins have been developed. Biosynthesis metabolic pathways can now be engineered providing alternative production routes for toxins. This could be particularly important in the case of those toxins that are awkward to extract in large quantities from natural sources.

Shortcomings in the quality assurance of current detection capacities have revealed vulnerability in our ability to deter or mitigate the use of toxins as weapons. Novel agents, or those with altered or enhanced characteristics have been identified or produced since the Seventh Review Conference.

Producing and stockpiling biological agents

- Since the Seventh Review Conference, there has been notable progress or changes in:
- **Concealing prohibited activities.** Changes to production signatures and a shift towards the use of multiple smaller reactors compromises efforts to identify sites of biological weapons production;
 - **Industrialising biological production processes.** Less space and time are now required for scale up, narrowing windows for interdiction. The process can also be simplified using new technologies, though at significant cost;
 - **Producing biological agents.** The increased use of biosynthesis and bio-based production, scaffolds, and ‘biopharming’ accelerates the speed and yield. This also applies to vaccine production;
 - **Switching production from permitted to prohibited activities.** The use of single-use, disposable and modular production equipment offers possibilities for faster technological breakout;
 - **Acquiring relevant equipment.** Critical laboratory materials such as reaction vessels (including those currently covered by control lists) can now be fabricated using 3-D printing technology, reducing the costs and potentially lowering barriers to prohibited activities. Once again, this complicates efforts to enforce non-proliferation measures.

- **Distributed production.** The decoupling of design and manufacture has led to the growth of stand-alone fabrication and production facilities. Whilst limited in number of geographic distribution at the moment at the moment, the potential for the growth of such facilities and their impact in changing the footprint of prohibited activities might warrant closer attention over the coming years;
- **Outsourcing biological production.** Multipurpose biological production facilities suitable for varying-scale production of biological agents as well as for the synthesis of genetic material and other synthetic genomics techniques are now commonplace. The existence of many ‘virtual’ biotech companies demonstrates the potential in this space;
- **Storing biological agents.** Increasing the environmental stability of biologics, together with the use of other approaches removes the requirements for cold-chain storage and its associated;
- **Infrastructure.** Improvements in production techniques have reduced the need for ‘stockpiling’ whilst the proliferation of freeze-drying capabilities enables this should it prove desirable.

Dispersal and delivery of biological agents

- Advances in several key areas now simplify the delivery a biological weapon:
- **Nanotechnology.** A wider range of nanoparticles, of different sizes, can more efficiently deliver complex payloads to diverse targets. Nanoparticles can now target previously inaccessible physiological sites and cell types (e.g. by crossing the blood-brain barrier). Nanoparticles also add other desirable characteristics to agents, such as increased persistence in the body and immune avoidance. Nanoparticles suitable for aerosol release have been developed since the Seventh Review Conference;

- **Aerobiology.** Offers powerful tools for modelling the release of bioweapons, including both environmental and indoor dispersal patterns, helping optimise the release of an agent. There have also been advances in equipment for generating and modelling aerosol dispersion have also been developed;
- **Use of chemical co-factors to increase the uptake of biological agents.** These have been identified for use with biologically active proteins; and
- **Increasing capacity to deliver biological weapons via the alimentary route.** The use of sophisticated formulations can improve absorption from the gastro-intestinal tract.

Increasing risks

- The conference identified a number of number of other key developments relevant to risk assessment relevant to the BWC, including:
- **Novel acquisition strategies.** The use of the ‘dark web’, biotechnology e-commerce or fabrication of biological agents from non-controlled parts, complicates non-proliferation obligations under Articles III and IV;
 - **Modification of pathogens or toxins.** This may confound identification and therapeutic intervention, thwarting efforts under Articles I, VII and X;
 - **The digitization of biology.** Publicly available data sets can be utilised to determine the feasibility of synthesising, thereby enabling a facile ‘proof of principle’, again complicating non-proliferation obligations under Article III; and
 - **Genome ‘editing’.** This can be used to modulate drug susceptibility in disease vectors, complicating efforts under Articles I, VII and X.

Further information

The information in this document is based on a Technical Report that includes fuller descriptions of the science and technology advances, an annotated bibliography and links to the research papers. The Technical Report can be accessed here:

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